PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
PAIK, Nam-Hoon

14th Fl., KTB Network Bldg., 826-14, Yeoksam-dong,
Kangnam-ku Seoul 135-769 Republic of Korea

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	07 APRIL 2005 (07.04.2005)
Applicant's or agent's file reference: 236	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR2004/003545	30 DECEMBER 2004 (30.12.2004)	30 DECEMBER 2003 (30.12.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC7 C07D 491/052

Applicant

SK CHEMICALS, CO., LTD. et al

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
LEE, Jae Jeong
Telephone No. 82-42-481-5604

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2004/003545

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material
   - ☐ a sequence listing
   - ☐ table(s) related to the sequence listing

   b. format of material
   - ☐ in wirtten format
   - ☐ in computer readable form

   c. time of filing/furnishing
   - ☐ contained in the international application as filed.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2004/003545

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1 - 4	NO
Inventive step (IS)	Claims		YES
	Claims	1 - 12	NO
Industrial applicability (IA)	Claims	1 - 21	YES
	Claims		NO

2. Citations and explanations :

Reference is made to the following documents:

D1: DONDONI et. al. `Model Studies toward the Synthesis of Dihydropyrimidinyl and Pyridyl α- Amino Acids via Three-Component Biginelli and Hantzsch Cyclocondensations` In: Journal of Organic Chemistry, 2003, 68(16), p.6172-6183
D2: El-Sedawy et. al. `Metabolism of Swertiamarin from Swertia japonica by Human Intestinal Macteria` In: Planta Medica, 1989, 55(2), p.147-150
D3: TADA et. al. `Modification of Pyridine-3-carboxamide (Nicotinamide) by Radical Substitution` In: Journal of Heterocyclic Chemistry, 1989, 26(1), p.45-48
D4: POPOV et. al. `In vitro Transformations of Gentiopicroside and Swertiamarin` In: Journal of Natural Products, 1988, 51(4), p.765-768

The present invention relates to novel pyridine derivatives having an inhibitory effect on production of cytokines, which are known to be involved in inflammatory responses, thus being useful as therapeutic agents for treating diseases related to inflammation, immune, chronic inflammation as well as an agent having an antiinflammatory and analgesis effect. Further, this invention relates to a method of manufacturing the same and a pharmaceutical composition containing the same.

D1 describes a novel and versatile strategy for the synthesis of heterocyclic α -amino acids. Incorporation of the 4-pyridyl-α -alanine derivative into a peptide chain is also described. D2 relates to the biotransformation of swertiamarin, a seco-iridoid glucoside isolated from Swertia japonica. Three metabolites are isolated and identified as erythrocentaurin, 5-hydroxymethylisochroman-1-one, and gentianine. D3 discloses modification of pyridine-3-carboxamide (nicotinamide) by radical substitution. D4 provides in vitro transformations of gentiopicroside and swertiamarin. Gentiopicroside are treated with NH_3 in EtOH to give gentanine and gentianidine. Gentanine are also prepared from swertiamarin and NH_3.

1. Novelty

The subject matter of claims 1-4 is already known from D1 (compound 34), D2 (compound 4), D3 (compound 12) and D4 (compound 3). Thus, claims 1-4 are neither novel nor inventive (PCT Article 33(2) and (3)).

2. Inventive Step

The novel derivatives of pyridine, and preparation methods of the same described in this application (the subject matter of claims 1-12) are generally known from D1 - D4. Documents D1 - D4 do not individually disclose all of the features of the present invention, but it would have been obvious to a person skilled in the art to disclose most of the features of the present invention by combining D1 to D4. Therefore, claims 1-12 lack an inventive step under PCT Article 33(3).

3. Industrial Applicability

The invention claimed in claims 1-21 can be used in the industry. Therefore, claims 1-21 are industrially applicable according to PCT Article 33(4).

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PAIK, Nam-Hoon
14th Fl., KTB Network Bldg.
826-14 Yeoksam-dong,
Kangnam-ku
Seoul 135-769
Republic of Korea

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)* 3 May 2006 (03.05.2006)	
Applicant's or agent's file reference 236	**REPLY DUE** within 2 months/~~days~~ from the above date of mailing
International application No. PCT/KR 2004/003545	International filing date *(day/month/year)* 30 December 2004 (30.12.2004)
Priority date *(day/month/year)* 30 December 2003 (30.12.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC[8]: ***C07D 491/052*** (2006.01)	
Applicant SK CHEMICALS CO. LTD.	

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

   I. ☒ Basis of the opinion

   II. ☐ Priority

   III. ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV. ☐ Lack of unity of invention

   V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI. ☐ Certain documents cited

   VII. ☐ Certain defects in the international application

   VIII. ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30.04.2006.

Name and mailing address of the IPEA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/200	Authorized officer GÖRNER W. Telephone No. 1/53424/558

Form PCT/IPEA/408 (cover sheet) (July 1998)

WRITTEN OPINION

International application No.
PCT/KR 2004/003545

I. Basis of the opinion

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1, 3 to 10,12 to 17,19 to 26, 28 to 89, 91, 92, 96 to 102, 104 , as originally filed
pages 18, 18a , filed with the demand
pages 2, 2-1, 11 to 11-5, 27, 90 to 90-38, 93, 95, 95-1, 96, 96-10, 104 to 104-4 , filed with the letter of 30 March 2006 (30.03.2006).

☒ the claims:
pages 105 to 110, 112 to 116 , as originally filed
pages , as amended (together with any statement) under Article 19
pages , filed with the demand
pages 112 to 112-5, 118 , filed with the letter of 30 March 2006 (30.03.2006).

☐ the drawings:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages .

☐ the claims, Nos. .

☐ the drawings, sheets/fig .

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as „originally filed".*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	—	YES
	Claims	1-21	NO
Inventive step (IS)	Claims	—	YES
	Claims	1-21	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims	—	NO

Citations and explanations

Table of amended pages and page numbers in accordance with the marked-up version of the application (30.03.2006).

Amended pages 2 and 2-1 replace originally filed page 2. Description continues with originally filed page 3. (Marked-up version page 2)

Amended pages 11 to 11-5 replaces originally filed page 11. Description continues with originally filed page 12. (Marked-up version pages 11-16).

Amended pages 18 and 18-a replace originally filed page 18. Description continues with originally filed page 19 (Marked-up version pages 23-25).

Since in the context of the originally filed text of the description the text flow generated by insertion of amended pages 27 and 27-1 is unclear, the originally filed page 27 was not exchanged for the amended pages 27 and 27-1. The term "arteriosclerosis", being the only difference between the amended and originally filed pages, is instead introduced between the terms "dermatomyositis" and "vasculitis" of the originally filed page 27 in accordance with amended page 27 (and marked-up version page 32).

Amended pages 90 to 90-38 replace line 20 ff of originally filed page 89 to line 19 of originally filed page 90. Description continues with originally filed page 90 line 20. (Marked-up version pages 94 – 133).

Amended page 93 replaces originally filed page 92 from line 10 ("human whole blood ...") and originally filed page 93 line 1-19 (due to a text break otherwise generated).
Description continues from originally filed page 93 line 19 with amended page 95. (Marked-up version pages 134-136).

Amended pages 95, 95-1, 96 and 96-1 replace originally filed pages 94 and 95. Description continues with originally filed page 96. (Marked-up version pages 136-139)

Amended Pages 104 to 104-4 replace originally filed page 103. The description is continued with originally filed page 104. (Marked-up version pages 147-151).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V (page 1)

Amended Pages 112 to 112-5 replace page 111 of the originally filed application. The claims continue with the originally filed page 112. (Marked-up version pages 158-163).

Originally filed page 117 was replaced by amended page 118. (Marked-up version pages 168-169).

Documents D1-D4 cited in the WO of the international search authority:
D1: Dondoni A, et al. "Model studies toward the synthesis of dihydropyrimidinyl and pyridyl alpha-amino acids via three-component Biginelli and Hantzsch cyclocondensations." J Org Chem. 2003 Aug 8;68(16):6172-83.

D2: El-Sedawy AI, et al. "Metabolism of swertiamarin from Swertia japonica by human intestinal bacteria." Planta Med. 1989 Apr;55(2):147-50.

D3: Tada et al. „Modification of pyridine-3-carboxamide (Nicotinamdie) by radical substitution" Journal of heterocyclic chemistry, 1989, 26(1), p45-48

D4: Popov et al. "In vitro transformations of gentiopicroside and Swertiamarin." Journal of natural products 1988, 51(4), p 765-768

Statement on the introduction of novel compounds according to the general formula in claim 1 through amendments
The amended examples of preparations (examples 145 – 231), compounds (claim 4) and illness (Claim 21) do not exceed the scope of the originally filed application in accordance with the general formula of claim 1 or the claimed biochemical effects (anti-inflammatory) of the named compounds regarding the illness "arteriosclerosis".
Nevertheless, it has to be stated that the introduction of compounds which were only disclosed by a general formula in the originally filed application or the introduction of further examples for preparations or an additional illness through amendments, may not be allowable in application procedures before the national patent offices.

The establishment of novelty, inventive step and industrial applicability was based on documents D1-D4 cited in the WO of the international searching authority and the amended version of the originally filed application (according to the letter of 30.03.2006).

1 — 4

Novelty and inventive step
The applicant issues the deletion of the novelty destroying compounds described in documents D1-D4 in the inventor's opinion from 27.10.2005. However, according to the formulation of the amended version of the claims and the dependencies of the claims in the amended version, the teachings of the cited documents D1-D4 are still within the scope of claims 1-21, since Documents D1-D4 describe compounds comprised by the general formula of claim 1.
The compounds described in documents D1-D4 are therefore novelty destroying for the amended version of claims 1-3 and 5-21.
The amended version of Claim 4 still comprises compound 3 (page 107, line 9) described in document D4 and compound 4 (page 107, line 10) described in document D2. In the light of documents D2 and D4, amended Claim 4 is therefore neither novel nor inventive.
In the light of documents D1-D4, the amended version of claims 1-21 are neither novel nor inventive.
In this context, it was not required to consider the inventor's opinion from 27.10.2005 regarding the inventiveness of the amended claims 1-21.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V (page 2)

Industrial applicability
Industrial applicability of the subject matters of claims 1-21 is given.